

Open Label study of subcutaneous immunoglobulin (SCIg) in myasthenia gravis

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### 3.1. Summary of Specific Aims

Little is known about subcutaneous immunoglobulin (SCIg) in myasthenia gravis (MG). A Pubmed search using the search terms myasthenia and subcutaneous immunoglobulin yields no relevant study. A prior controlled study found that intravenous immunoglobulin (IVIg) -treated (2 g/kg of IVIg) MG patients with progressive symptoms experienced a clinically meaningful improvement in the quantitative myasthenia gravis (QMG) score at day 14 which persisted at day 28.<sup>1</sup> More recently, IVIg was found to have comparable efficacy to plasma exchange (PLEX) in the treatment of patients with moderate to severe MG defined as QMG > 10.5.<sup>2</sup> As part of routine clinical care, we have treated MG cases with chronic outpatient IVIg. In those patients, SCIg would be easier to administer and foster more patient independence. We propose the hypothesis that SCIg is as effective as IVIg in controlling MG in patients transitioning from intravenous (IV) to subcutaneous (SC) mode of administration. We also hypothesize that the SCIg is safe and well tolerated in MG cases. There is some data from SCIg in other neuromuscular disorders the SCIg may be better tolerated than IVIg.

The primary objective is to measure the efficacy of SCIg in the 12-week experimental treatment phase (Week 0 to Week 12) of MG subjects who are stable after completing the IVIg screening phase (Week minus 9 [-9] to Week 0). Disease stability in the screening phase is considered a change of no more than 3 points increase in the QMG score at Week 0 as compared to Week -9. The primary outcome is after the screening phase and is the percent of subjects enrolled in the experimental treatment phase of SCIg experiencing an increase of no more than 3 points in the QMG score from baseline (Week 0) to Week 12 visits of SCIg open label therapy.

The secondary objectives are:

- 1) To further assess the efficacy of SCIg in MG
- 2) To assess the safety and tolerability of SCIg in subjects with MG
- 3) To evaluate whether SCIg can result in stable IgG antibody levels

The secondary outcome measures include the change:

1. from baseline (Week 0) to Week 12 in myasthenia activities of daily living (MG-ADL), myasthenia gravis 15 item quality of life survey (MG QOL-15), MG composite score, and treatment satisfaction questionnaire for medication (TSQM) in completers of the experimental treatment phase
2. from week -10 to week 12 in the safety profile between intravenous screening phase and subcutaneous experimental treatment phase as measured by abnormalities on routine safety laboratory parameters (CBC, differential and comprehensive chemistry profile) and overall rate, severity and treatment-relatedness of any adverse event.
3. from week -10 to week 12, IgG level between intravenous screening phase and subcutaneous experimental treatment study phase

### 3.2. Background, Prevalence and Significance:

Prevalence:

Myasthenia gravis (MG) is a rare neuromuscular disorder. The estimated prevalence is 20/100,000.<sup>3</sup> Using this prevalence, we estimate the MG population in US to be 60,000 based on a US population of 300,000,000. A wide range of incidence is reported with an estimate of about 2.0 to 10.4/million/year in Virginia<sup>4</sup> to 21.27/million/year in Barcelona,

Spain.<sup>5</sup> In patients younger than 40, women predominate with a ratio of 7:3. In the fifth decade, new cases of MG are evenly distributed between men and women. After age 50, new cases of MG are slightly more common in men with a ratio of 3:2.<sup>6-7</sup>

*Background and Significance:*

Myasthenia gravis is characterized by weakness and fatigability of ocular, bulbar, and extremity musculature.<sup>8-12</sup> The “fatigue” of MG can be analyzed electrophysiologically by demonstrating a decremental response of the compound motor action potential to repetitive nerve stimulation.<sup>13</sup> The improvement of strength with reversible anti-acetylcholinesterase drugs such as edrophonium, physostigmine, and pyridostigmine was the first evidence implicating the neuromuscular junction in the pathogenesis of MG.<sup>14</sup>

The autoimmune nature of MG was established by producing experimental allergic MG (EAMG) through the immunization of animals with purified acetylcholine receptor (AChR) in addition to exhibiting clinical and electrophysiological similarities with human MG. Subsequently, circulating AChR antibodies (Abs) were found to be present in the serum of patients with MG<sup>15</sup> and passive transfer of human serum to healthy rodents produced clinical evidence of MG in animals.<sup>16</sup>

Therapeutic initiatives in MG have focused on ways of either increasing the amount of acetylcholine in the synaptic cleft or suppressing the aberrant immune response.<sup>12,17-18</sup> The first effective treatment of MG involved the administration of an acetylcholinesterase inhibitor to increase the amount of acetylcholine available for binding in the neuromuscular junction<sup>14</sup>. This approach, while effective in mild cases of MG, is directed only toward the control of symptoms and does nothing to alter the pathophysiology of the disease.<sup>12,17-18</sup>

A number of attempts have been made to suppress the immune system and the associated antibody response. Thymectomy was first performed more than a half-century ago and was the earliest form of immune-directed therapy in MG.<sup>19</sup> While there is evidence for involvement of the thymus in the autoimmune response in MG, less than one-third of patients who have undergone thymectomy enter remission.<sup>20-21</sup>

The introduction of corticosteroids in the therapy of MG was a major clinical advance. Prednisone is the most commonly used corticosteroid<sup>22</sup> and has been associated with an improvement in half<sup>23</sup> and a clinical remission in more than a quarter of patients. As a result, steroids are often considered the immunotherapeutic of choice in patients who remain symptomatic on pyridostigmine. Many patients, however, can never be weaned completely from steroid therapy.<sup>23</sup> Corticosteroids exert a variety of effects on the immune system, but the exact mechanism of action in MG has yet to be defined. However, corticosteroids have dose-limiting side effects such as generalized immunosuppression, hyperglycemia, hypertension, myopathy, weight gain, cataracts, and osteoporosis.

Other approaches to immunosuppression have come into clinical use in recent years. Drugs such as azathioprine,<sup>24-25</sup> cyclophosphamide,<sup>26</sup> cyclosporine,<sup>27-28</sup> mycophenolate mofetil,<sup>29-32</sup> and intravenous immunoglobulin (IVIg)<sup>1-33</sup> have been studied with varying degrees of success. We are completing a study of methotrexate in MG<sup>34</sup>  
<http://clinicaltrials.gov/ct2/show/NCT00814138>.

IVIg is an approved treatment for several immunodeficiency syndromes<sup>35-38</sup> and more recently has been approved for the management of two other autoimmune neuromuscular

disorders, chronic inflammatory demyelinating polyneuropathy (CIDP)<sup>39</sup> and multifocal motor neuropathy.<sup>40</sup> Intravenous immunoglobulin (IVIg), a pooled gammaglobulin product from several thousand blood donors, has a complex immunomodulatory mechanism of action. It is thought to involve pathogenic autoantibody production modulation and binding inhibition, pro-inflammatory cytokinesuppression, Fc receptor blockade, macrophage colony stimulating factor and monocyte chemotactant protein-1 increase, alteration in T cell function, decrease in circulating CD54 lymphocytes, and inhibition of cell transmigration into the muscle.<sup>41</sup> More recently, investigators from the Rockefeller found that Fc core polysaccharide 2,6-sialylation mediates the anti-inflammatory properties of IVIg.<sup>42</sup>

IVIg is administered as an induction dose of 2 gm/kg over 2 to 5 days, followed by monthly maintenance doses of 0.4- 2.0 gm/kg given every 2 to 4 weeks. While it is generally infused no faster than 150 to 200 cc/h, a recent report described infusion rates of up to 800 cc/h in 50 patients, which was reasonably well tolerated.<sup>43</sup> Lee and colleagues treated two CIDP patients with subcutaneous infusion of immunoglobulins (SCIg) after IVIg therapy was shown to be effective.<sup>44</sup> Application of SCIg was well tolerated and led to stabilization of the disease course.<sup>44</sup> A study of SCIg IgPro20 in CIDP is currently ongoing <http://clinicaltrials.gov/ct2/show/NCT01545076>.

IgPro20 (Hizentra®) is a ready-to-use formulation of human IgG with ≥98% purity for subcutaneous (SC) administration. It is approved in the United States of America (US), in the EU, in Switzerland, and in Canada under the brand name Hizentra® for SC application in primary immune deficiency (PID) syndromes and is manufactured at CSL Behring's (CSLB's) facility in Berne, Switzerland. It is a 20% liquid formulation (200 mg/mL) of human normal immunoglobulin for subcutaneous use administered SC weekly or biweekly (ie-using 2x the weekly dose). Bioavailability and pharmacokinetics of SCIg and intravenous IgG (IVIg) differ in patients with primary immunodeficiencies. Based on area under the curve (AUC) of serum IgG versus time and trough level ratios (TLRs) on SCIg/IVIg, the mean dose adjustments required for non-inferior AUCs with multiple different SCIg preparations were 142% (± 11, with no real difference between different preparations.<sup>45</sup> However, there were wide variations between adjustments required by different subjects. Combined data from multiple studies allow estimation of the ratio of IgG levels with different dose adjustments, and of the steady state serum levels with different SCIg doses. When switching a patient from IVIg to SCIg, individualizing the dosage based on measured serum IgG levels and the clinical response is preferable to using mean pharmacokinetic parameters.<sup>45</sup> In a prospective, open-label, multicentre, single-arm, phase III clinical trial conducted in the US, the mean SC IgPro20 : IV IgPro10 dose ratio (dose adjustment coefficient) was 1.53 (range 1.26-1.87). The resulting mean AUCs were 105.6 g · day/L for IgPro20 versus 103.2 g · day/L for IgPro10 (geometric mean ratio 1.002; lower one-sided 95% confidence limit [CL] 0.951). Thus, the primary endpoint of the study was met, as this result exceeded the pre-specified criterion of the lower one-sided 95% CL of ≥0.8 for non-inferiority. At these AUCs, which were considered equivalent, the mean serum IgG trough level on SC IgPro20 was 129% of that on IV (range 1.18-1.73). Titers of specific antibodies tested were well above respective product specifications, suggesting that protection against infection would be effective.<sup>46</sup>

Little is known about SCIg in myasthenia gravis (MG). A Pubmed search using the search terms myasthenia and subcutaneous immunoglobulin yields no relevant study. A prior controlled study found that IVIg-treated (2 g/kg of IVIg) MG patients with progressive symptoms experienced a clinically meaningful improvement in the QMG score at day 14 which persisted at day 28.<sup>1</sup> More recently, IVIg was found to have comparable efficacy to

PLEX in the treatment of patients with moderate to severe MG defined as QMG > 10.5.<sup>2</sup> As part of routine clinical care, we have treated MG cases with chronic outpatient IVIg. In those patients, SCIg would be easier to administer.

Data on SCIg use is limited in MG. In a review of IVIg dispensing records of a specialty pharmacy, forty-six patients (median age, 56.5 years; range, 8-86 years) fulfilled the inclusion criteria. Thirty-one patients with CIDP received IgG at 7- to 92-day intervals (mean [standard deviation (SD)], 28 [16] days). The mean (SD) IgG dose was 75 (60) g/dose, equivalent to 866 (623) mg/kg/dose and 1145 (778) mg/kg/month. Six patients with stable MG received IVIg or subcutaneous IgG at 3.5- to 61-day intervals (28 [20] days) at a mean (SD) IgG dose of 39 (15) g/dose, equivalent to 405 (108) mg/kg/dose and 783 (680) mg/kg/month. One patient with CIDP and 4 patients with MG were treated with weekly subcutaneous IgG injections.<sup>47</sup>

### 3.3. Preliminary Studies

While little is known about SCIg in myasthenia gravis (MG) and even though IVIg is not FDA-approved in MG, two class 1 studies suggest IVIg is efficacious in MG.<sup>1,2</sup> As part of routine clinical care, we have treated MG cases with chronic outpatient IVIg. In those patients, SCIg would be easier to administer.

A prior randomized, placebo-controlled, masked study aimed to determine the effectiveness of IVIg in MG patients with worsening weakness.<sup>1</sup> Fifty-one patients with worsening weakness due to MG were randomized to infusion with 2 g/kg of IVIg or an equivalent volume of IV dextrose 5% in water. The Quantitative Myasthenia Gravis (QMG) Score for Disease Severity, a validated clinical composite scale, was calculated by a masked observer at baseline and days 14 and 28. In IVIg-treated patients, a clinically meaningful improvement in QMG Score for Disease Severity was observed at day 14 and persisted at day 28. The greatest improvement occurred in patients with more severe disease as defined by a QMG Score for Disease Severity greater than 10.5.

More recently, 84 patients with moderate to severe MG defined as QMG>10.5 and worsening weakness were randomized to receive IVIg, 1 g/kg/day for 2 consecutive days, or plasmapheresis (PLEX), 1.0 plasma volume exchanges for 5 exchanges.<sup>2</sup> The patients were evaluated at day 14 after treatment for the primary efficacy parameter of change in QMG and secondary clinical and electrophysiologic parameters and were followed for a total of 60 days.

Both IVIg and PLEX reduced the QMG, and IVIg was comparable to PLEX in efficacy. The presence of AChR Abs and greater baseline disease severity predicted a better response to therapy. The post intervention status revealed that the same proportion of patients improved with treatment: 69% on IVIg and 65% on PLEX. The duration of improvement was similar with both treatments and both treatments are well-tolerated.

#### *Previous Clinical Trials Experience*

The principal investigator and the co-investigators have extensive experience in treatment trials in a variety of neuromuscular diseases including myasthenia gravis, amyotrophic lateral sclerosis, muscular dystrophies, inflammatory myopathies, and peripheral neuropathies. All sites have expertise in MG research and four of the participating sites were in the recently completed investigator-initiated study of mycophenolate mofetil in MG.<sup>29,32</sup> Two centers were

sites in the simultaneous mycophenolate mofetil industry-sponsored mycophenolate trial.<sup>30-31</sup> All of the centers are currently sites for the ongoing NIH-sponsored prospective trial of thymectomy in MG.<sup>33</sup> Dr. Barohn was on the steering committee for this federally funded study. Four sites have participated in the federally-funded trial of methotrexate in MG. These centers are experienced in recruiting and enrolling patients into clinical trials. In addition, all of the centers are accustomed to working together as a group in clinical trials.

All of the study sites are regional referral centers for patients with neuromuscular diseases, and in specific, for myasthenia gravis. Each site has relatively large populations of MG patients from which to draw upon for patient enrollment.

### 3.4. Methods, Expected Results, Data Analysis, Interpretations, and Significance

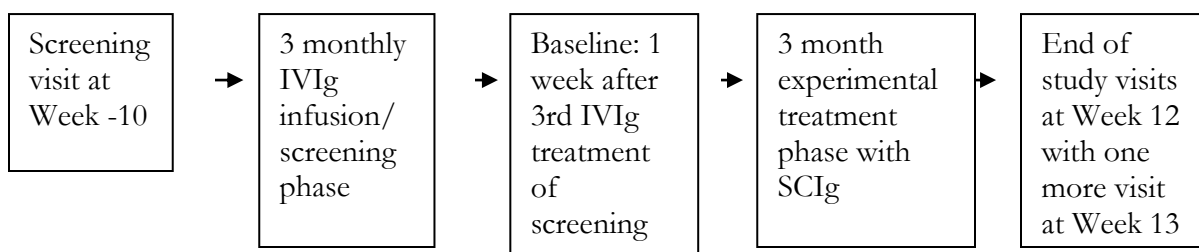
#### *Study Design*

This is a phase-2 multi-center (5 sites) study to assess the efficacy and safety of SCIg in the experimental treatment phase in 20 MG patients who remain stable. We define stability while receiving IVIg as the QMG score not increasing by more than 3 points at week 0 compared to week -9. We anticipate a 20% drop out rate in the IVIg screening phase such that 20 subjects will remain out of the 25 initial MG cases.

Twenty-five subjects receiving IVIg as their current treatment are enrolled into the IVIg screening phase. At least 20 subjects are expected to continue to the experimental treatment phase and qualify based on QMG stability for a baseline visit at week 0. The 20-25 subjects will then receive weekly SCIg using a 1:1.2 dosing ratio to IVIg. For example, a 100 kg subject receiving IVIg dose of 1 gm/kg every 4 weeks would be converted to a 20% higher dose of SCIg dose weekly = 30 grams (150 mL) per week.<sup>46</sup> We will report serious adverse events if they occur during the study using the FDA guidance *Safety Reporting Requirements for INDs and BA/BE Studies*.

(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm227351.pdf>).

#### *Study Graphic:*



#### *Screening Phase on IVIg:*

Subjects will be infused with Privigen at the same dose that was being given for routine ongoing care. This will range from a dose of 0.2 to 2 gm/kg/4 weeks. If a subject is on an IVIg dosing frequency other than 0.2 to 2 gm/kg/4 weeks the dose will be converted to the equivalent dose for every 4-week administration.

#### *Experimental Treatment Hizentra® Administration:*



We will start by estimating that the maximum weight based on which we propose to treat myasthenia gravis (MG) subjects is 100 kg. Furthermore, the maximal dose of IVIg of 2 g/kg/month converts to 0.5 g/kg/week. Therefore, the maximal IVIg weekly treatment in any subject is 50 grams per week. In order to be converted to bioequivalent SC route, the dose will be 20% higher (60 grams per week) and ramp if needed in the second month up 37% higher (about 68.5 grams per week) and if needed in the third month up to 50% higher (75 grams per week). This translates into a maximum initial SC weekly volume of 312.5 cc starting on Week 0 which may be increased by the investigator to 375 cc per week at Week 4.

The maximum dose we think a subject may need, as outlined above is 3 ml/kg to 3.75 ml/kg. With the current limit of 25 ml per site in the package insert (PI) that will require a lot of needles per week. More specifically and assuming 4 injection sites per day (max. 100 cc/day), subjects would ultimately need 4 infusion days, each day about 80 to 95 cc divided over 4 sites. For an injection site map see Appendix 1.

There are two other studies of Hizentra® in which the FDA has allowed for volumes larger of 40 ml per site than the PI lists:

- 1) Hizentra CIDP IND (IND # 14694, pivotal Study IgPro20\_3003 with 40 mL/site allowed; study ongoing) <http://clinicaltrials.gov/ct2/show/NCT01545076>
- 2) Hizentra Primary Immune Deficiency (PID) IND (IND # 13021, US Extension Study IgPro20\_3001 with 40 mL/site allowed; study completed). The final CSR for this extension study was submitted to the IND only (IND 13021, serial #61 on 30 Sep 2011).

We would like to allow the subjects in this study to go up to 50 cc/site, to allow the regimen to be more practical and convenient for them, and we have included the following plan to allow the subjects to increase to that volume under supervision and with repeated examinations to be sure there are no safety problems with that regimen. At the maximal 50 cc per site and assuming 4 injection sites per day (max. 200 cc/day), we would need 2 infusion days, each day consisting of 157 to 188 cc divided about over up to 4 sites. At a maximum rate of 25 ml/hr/site, that could conceivably allow a subject like that to infuse for 2 hrs twice a week. The infusion sites would only need to be 2 inches apart, and by the 3rd day, we should be able to use the same site again. For patients that do not tolerate the 50 cc per site approach as determined by the local investigator team, we could do infusions over 3 days with each SC infusion site being no more than 40 cc per site. We are proposing allow subjects to ultimately go up to 50 ml per site and accomplish their weekly dosing in 2 hrs twice a week, after a ramp-up. A recent update in the IgPro20 package insert outlines the potential dosing frequency of 2-7 times per week. Below is a chart with guidance on SC infusion parameters for volume per site as patients receive each subsequent infusion.

Infusion Parameters*	Infusion Number			
	1 <sup>st</sup>	2 <sup>nd</sup> to 4 <sup>th</sup>	5 <sup>th</sup>	6 <sup>th</sup> and above
Volume (mL/site)	≤ 15		≤ 20	≤ 25
Rate (mL/hr/site)	15	≤ 25		

Below is an example of a conservative slower titration rate. Patients who tolerate the SCIg administration can be titrated up at the investigators discretion at a faster rate. Volume per site and number of infusions per week may be escalated or reduced during the course of the

experimental treatment phase based on patient's tolerability and the local site investigator judgment as long as the weekly dose is maintained.

I. SCIg Week 0

One week after the last IVIg dose and as per package insert, SC infusions would start at 15 cc per site x 4 sites (60 cc daily) maximum rate = 15 ml/hr/site and are spaced out over 4 days in the first week. The first 2 infusions are for training purposes done under nurse supervision in the research facility. It is anticipated the subject will demonstrate competency and be eligible to self-administer the next 2 infusions in the home setting.

II. SCIg Week 1

At 72 hours or more after the last infusion, the subject skin is inspected by the local investigator or nurse. For example, if the last infusion of the first week was given on Friday, the sites would be examined on Monday. If there is no residual reaction at sites other than mild erythema or induration, the volume per site would be advanced, as tolerated. Therefore, by the 5th infusion, this can be increased by the local investigator team (physician or nurse) to 20 ml per site at the research unit. The next 3 infusions are done at home by the subject during the rest of Week 1.

III. SCIg Week 2

If there is no significant local site residual reaction at 72 or more hours after the last infusion as judged by phone discussion between the nurse and the patient, the volume per infusion in Week 3 can be increased to 25 ml/site (100 cc per 4 sites) on the first day followed on the next 2 days and as tolerated by 2 other sets of infusions of 100 cc each over 4 other sites to reach a total of 300 cc in Week 2. These infusions are done at home by the subject during Week 2.

IV. SCIg Week 3

If there is no significant residual reaction at sites at 72 or more hours after the last infusion as judged by phone discussion between the nurse and the patient, the volume per infusion in Week 3 can be increased to 30 ml/site (120 cc daily) on the first day followed on the next 2 days and as tolerated by 2 other sets of infusions of 120 cc each over 4 other sites to reach a total of 360 cc in Week 3. These infusions are done at home by the subject during Week 3.

Therefore, the maximum total volume in the first month of SCIg for a 100-kg subject would still be up to 1,220 cc which is equivalent to 244 grams of Ig or a mean weekly dose of 61 grams of SCIg.

**This would accommodate amply the 1:1.20 conversion factor target since this factor would yield 60 grams per week...**

V. SCIg Week 4 to Week 7:

The next decision step at Week 4 depends on the patient MG status as judged by the local site investigator.

A) If MG is stable as judged by the site investigator: a 100-kg subject would stay on the dose of approximately 60 to 62.5 grams per week or 300 to 312.5 cc per week:

1. If there is no significant residual reaction at sites at 72 or more hours after the last infusion:

a. Week 4: If there is no significant residual reaction at sites at 72 or more hours after the last infusion, the volume per infusion can be increased to 35 ml/site (140 cc daily) after site inspection by the local

- investigative team (physician or nurse). A second infusion is repeated on the next day at home by the subject during Week 4.
- b. Week 5: If there is no significant residual reaction at sites at 72 or more hours after the last infusion as judged by phone discussion between the nurse and the patient, the volume per infusion can be increased to 40 ml/site (160 cc daily). These infusions are done at home by the subject.
  - c. Week 6 (new in-person safety visit): If there is no significant residual reaction at sites at 72 or more hours after the last infusion, the volume per infusion can be increased to 45 ml/site (180 cc daily) after site inspection by the local investigative team (physician or nurse). A second infusion is repeated on the next day at home by the subject during Week 6.
  - d. Week 7: If there is no significant residual reaction at sites at 72 or more hours after the last infusion as judged by phone discussion between the nurse and the patient, the volume per infusion can be increased to 50 ml/site x 3 sites (150 cc daily) by the seventh week. These infusions are done at home by the subject during Week 7.

The maximum total volume in the second month of SCIg for a 100-kg subject would be 1,260 cc which is equivalent to 252 grams of Ig or a mean weekly dose of 63 grams of SCIg.

- 2. If the skin reaction does not allow for an increase in volume per site, the 100-kg subject would continue on SCIg 100 cc three times per week which means that the per site infusion volume would be reduced from 30 cc per site to the FDA labelling of 25 cc per site.

The maximum total volume in the second month of SCIg for a 100-kg subject would be 1,200 cc which is equivalent to 240 grams of Ig or a mean weekly dose of 60 grams of SCIg.

A re-challenge can be attempted again once during the study per IV and V. A) 1. above.

- B) If the site investigator assesses that the MG is not stable and that the patient is safe to continue in the study, the 100-kg subject would increase the dose to approximately 68.5 grams per week or 342.5 cc per week:
  - 1. If there is no significant residual reaction at sites at 72 or more hours after the last infusion:
    - a. Week 4: If there is no significant residual skin reaction, the volume per infusion can be increased to 35 ml/site (140 cc daily) after site inspection by the local investigative team (physician or nurse). A second (140 cc) and third infusion (70 cc) is repeated over the next 2 days at home by the subject during Week 4.
    - b. Week 5: If there is no significant residual reaction at sites at 72 or more hours after the last infusion as judged by phone discussion between the nurse and the patient, the volume per infusion can be increased to 40 ml/site (160 cc daily). A second infusion is repeated on the next day at home by the subject during Week 5. These infusions are done at home by the subject.
    - c. Week 6 (new in-person safety visit): If there is no significant residual reaction at sites at 72 or more hours after the last infusion, the volume per infusion can be increased to 45 ml/site (180 cc daily) after site inspection by the local investigative team (physician or nurse). A

- second infusion is repeated on the next day at home by the subject during Week 6.
- d. Week 7: If there is no significant residual reaction at sites at 72 or more hours after the last infusion as judged by phone discussion between the nurse and the patient, the volume per infusion can be increased to 50 ml/site x 4 sites (200 cc day one and 150 cc day two) by the seventh week. These infusions are done at home by the subject during Week 7.

The maximum total volume in the second month of SCIg for a 100-kg subject would be 1,380 cc which is equivalent to 276 grams of SCIg per month or a mean weekly dose of 69 grams of SCIg.

**This would be more than ample to meet the 1:1.37 conversion factor target since this factor would yield 68.5 grams per week.**

2. If the skin reaction does not allow for an increase in volume per site, the per site infusion volume would be reduced from 30 cc per site to the FDA labelling of 25 cc per site. A 100-kg subject would continue on SCIg 100 cc but the frequency would have to be increased to four times per week alternating with three times a week.

The maximum total volume in the second month of SCIg for a 100-kg subject would be 1,400 cc which is equivalent to 280 grams of SCIg per month or a mean weekly dose of 70 grams of SCIg.

A re-challenge can be attempted again once during the study per section IV and V. B) 1. above.

#### VI. SCIg Week 8 to Week 12:

The next decision step at Week 8 depends on the patient MG status as judged by the local site investigator.

A) If MG is stable as judged by the site investigator: a 100-kg subject would stay on the dose of approximately 68.5 grams per week or 342.5 cc per week.

- 1) If the skin reaction at 72 hours allows for a volume per site higher than 25 cc, the volume per infusion site may be up to 50 ml/site x 3 to 4 sites (150 cc one day and 200 cc on the other day weekly) by the eighth week with 2 infusion days per week. These infusions are also done at home by the subject Week 8 to Week 12.

The maximum total volume in the third month of SCIg for a 100-kg stable subject would be 1,400 cc which is equivalent to 280 grams of SCIg per month or a mean weekly dose of 70 grams of SCIg. This would be more than ample to meet the 1:1.37 conversion factor target since this factor would yield 68.5 grams per week.

- 2) If the skin reaction does not allow for a volume per site higher than 25 cc, the 100-kg subject would continue on SCIg 100 cc three to four times per week which means that the per site infusion volume would be at the FDA labelling amount of 25 cc per site. A 100-kg subject would continue on SCIg 100 cc but the frequency would have to be increased to four times per week alternating with three times a week.

The maximum total volume in the third month of SCIg for a 100-kg subject would be up to 1,400 cc which is equivalent to 280 grams of Ig or a mean weekly dose of up to 70 grams of SCIg.

**This would accommodate amply the 1:1.37 conversion factor target since the factor would yield 68.5 grams per week.**

**A re-challenge can be attempted again once during the study per IV and V. B) 1. above.**

B) If the site investigator assesses that the MG is not stable in a patient who is experiencing a worsening that does not qualify as a clinical deterioration and that the patient is safe to continue in the study, the subject would continue on 1:1.37 IVIg to SCIg ratio and the investigator would follow the other recommendations for medication adjustment in the section titled “Subject deterioration, worsening, rescue medication and improvement”. More specifically, acceptable rescue medications include the initiation of prednisone or mestinon or an increase in prednisone or mestinon dose.

C) If the site investigator assesses that the MG is not stable in a patient who is experiencing a worsening that qualifies as a clinical deterioration (please refer to “Subject deterioration, worsening, rescue medication and improvement”), the subject will be withdrawn from the study and considered to be a treatment failure. Treatment of clinical deterioration is per standard of care with plasmapheresis or IVIg.

D)

1) Additional guidance and safeguards for dosing titration:

1. If subjects tolerate 50 ml/site, up to 4 sites (maximum of 200 ml) may be used per day. Rate should not exceed 25 ml/site/hr.
2. Subject may opt to stop advancing volume per site at any point, and/or may elect to go back to a smaller volume.
3. DSMB may stop this forced-upward titration of volume per site at any limit they feel is causing excessive numbers or severity of reactions or other forms of intolerance.
4. If any subject wishes to exceed 50 ml per site, limit of 200 ml per day, or rate of 25 ml/site/hr, this may be allowed at discretion of local investigator, after investigator certifies in subject record that subject has tolerated volumes and rates specified above.
5. Subject dose may be rounded to the nearest vials size (IgPro20 will be dispensed in 20ml vials).

VII. Home Administration:

Educating the patient regarding self-administration is essential to optimizing safety of SCIg therapy. The goal of therapy is for the MG patient to learn self-administration of SCIg therapy. Demonstrated proficiency by each study subject is accomplished by successful

return demonstration on self-administration of the SCIg therapy. Subjects will be provided with a self-administration teaching guide of Hizentra.

Since our study subjects will be using the Freedom-60 pump, they will be able to titrate the rate of infusion up or down for each infusion based upon their individual tolerability. The Freedom-60 flow rate tubing is the piece of equipment that regulates the infusion rate. The Freedom-60 pump is a mechanical pump and is simple to use, and does not have the ability to dial up or down a specific infusion rate. It is the Freedom-60 flow rate tubing that sets the rate during each infusion.

Based upon the total SCIg volume we prescribe weekly it will be easy to identify the number of SCIg sites and rate of infusion using the Freedom-60 calculator. We will obtain from RMS Medical the Freedom-60 calculator which automatically calculates / recommends the correct administration set (SCIg needle set) and flow rate tubing so that the nurse can provide the proper tubing and supplies to the patient.

*Baseline Visit:*

Subjects will then be converted over to 20% Hizentra® at a conversion ratio of IVIg:SCIg of 1 to 1.25. At baseline, the first dose is administered within one week from the third IVIg infusion of the Stabilization Phase. The drug is administered through a pump as outlined above depending on dose and tolerability and for 3 months duration.

*3-month Treatment Phase on SCIg:*

Nurse training of the patient will occur during Week 0/baseline visit. A portable infusion pump will be used to administer the SCIg therapy. Patients must be able to demonstrate proficiency in self-administration of the SCIg drug after teaching visits are completed. It is the expectation that patients will be able to administer SCIg therapy at home through the end of the study at Week 12. Another dose increase of 25% (1.20 to 1.37 at week 4) is allowed (total 150% of original IVIg dose) if a patient worsens and the principal investigator believes that it is in the best interest of the patient. Patients requiring increase in SCIg dose will undergo additional assessment at unscheduled visits.

*Timeline:*

This study will take place over 36 months. The first 12 months will center on full protocol development, IRB approval at all sites, contracting with CSL-Behring and contracting with other investigator sites, CRF development, database development, investigator meeting, project management and administrative activities. During the second year of this project investigators will focus on subject enrollment. Enrollment would proceed at the rate of 2 patients per month with 6 months study participation. After the last patient is completed, data clean up; lock and analysis would take place. Presentation at national/international meetings and publication preparation would be the final step followed by study closure.

*Study Eligibility*

*Inclusion Criteria:*

Patient selection will be based on a diagnosis of MG by all of the following specific criteria:

- 1) Patients 18 and older.

- 2) Patients must have prior or current documentation of MGFA MG grades 2, 3, or 4 generalized MG, according to the MGFA classification system.<sup>48</sup> These grades correspond to mild (2), moderate (3), and severe (4).
- 3) Elevated AChR or MuSK Ab. These tests will have been performed at some time prior to entry into the study. Double seronegative MG patients with prior documentation of an abnormal decrement (>10%) on slow repetitive nerve stimulation or an abnormal single fiber EMG will also be allowed to participate.
- 4) Patient's signs and symptoms should not be better explained by another disease process.
- 5) IVIg maintenance dose of 0.2 to 2 gm/kg/4 weeks or equivalent dose administered Q 2-4 weeks±3days
- 6) Stable IVIg for at least 3 cycles (definition of stability: no change in prescribed dosage or frequency by the treating physician)
- 7) Patient must be receiving no more than 200g/4weeks of IVIg.
- 8) Patients must be willing to complete the study and return for follow-up visits.
- 9) Patients must be willing to give written informed consent before participating in this study. A copy of the signed consent must be kept in the patient's medical record.
- 10) Patients can be on the following drugs as long as there has been no dose change for 60 days: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, tacrolimus, methotrexate or other immunosuppressive drugs.
- 11) Patients can be on prednisone as long as there has been no dose change for 30 days.

#### Exclusion Criteria:

- 1) MGFA grade V within 6 months of screening.
- 2) A history of chronic degenerative, psychiatric, or neurologic disorder other than MG that can produce weakness or fatigue.
- 3) Other major chronic or debilitating illnesses within six months prior to study entry.
- 4) Female patients who are premenopausal and are: (a) pregnant on the basis of a serum pregnancy test, (b) breast-feeding, or (c) not using an effective method of double barrier (1 hormonal plus 1 barrier method or 2 simultaneous barrier methods) birth control (birth control pills, male condom, female condom, intrauterine device, Norplant, tubal ligation, or other sterilization procedures).
- 5) Altered levels of consciousness, dementia, or abnormal mental status.
- 6) Thymectomy in the previous three months.
- 7) Evidence of renal insufficiency (Cr>1.5 x elevated) or liver disease (transaminases > 2.5 x elevation) at screening.
- 8) Skin disease that would interfere with assessment of injection site reaction
- 9) History of severe reactions to IVIg or SCIg.
- 10) Participation in a research study within the last 3 months
- 11) Treatment with rituximab or other biologics within 12 months of study entry
- 12) Inability to provide informed consent.
- 13) History of thrombotic episodes within the last year prior to enrollment
- 14) Known allergic or other severe reactions to blood products including intolerance to previous normal human immunoglobulin for intravenous administration (IVIg) and/or subcutaneous immunoglobulin (SCIg), such as history of clinically relevant hemolysis

- after IVIG infusion, aseptic meningitis, recurrent severe headache, hypersensitivity, severe generalized or severe local skin reaction.
- 15) History of IgA deficiency or evidence of IgA deficiency at screening.

### *Study Procedures (Table 1)*

A clinical evaluator (CE) will perform evaluations at the study visits. The CE can be a physical therapist, physical therapist assistant, nurse, or physician who is not one of the investigators. All CEs will have undergone extensive, standardized training in Quantitative MG and Activities of Daily Living scoring before the study is initiated. This training will be performed by the principal CE, Laura Herbelin, from the University of Kansas Medical Center. The evaluations performed by the CE will include:

- 1) A battery of quantitative functional tests from which a Quantitative MG score (QMG) is calculated. The QMG is a 13-item test that objectively measures ocular, bulbar, extremity fatigue/strength, and respiratory function.<sup>49-51</sup>
- 2) MG activities of daily living (MG-ADL) score. The MG-ADL is a subjective survey of the subject on how their activities of daily living are affected.<sup>52</sup> MG-ADL is still a relevant outcome measure.<sup>53</sup>
- 3) MG composite score. Specific components of the QMG, the MG-ADL, and the MMT are combined to obtain the MG composite score.<sup>54-55</sup>
- 4) MG quality of life-15 (MG QOL-15). A new MG-specific quality of life questionnaire that the subject fills out.<sup>56</sup>

The principal investigator or a co-investigator will perform the following procedures:

- 1) History
- 2) Physical examination
- 3) Neurological examination
- 4) Assign a MGFA MG grade.<sup>48</sup> The investigator will assign a MGFA clinical classification grade. The grades are Class I- Any ocular muscle weakness, may have weakness of eye closure, all other muscle strength is normal (subject will be excluded with this grade), Class II – Mild weakness affecting other than ocular muscles, may also have ocular muscle weakness of any severity. Class III – Moderate weakness affecting other than ocular muscles, may also have ocular muscle weakness of any severity. Class IV – Severe weakness affecting other than ocular muscles, may also have ocular muscle weakness of any severity. Class V – Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. Patients rated as Class V will be excluded.

The study coordinator will perform the following:

- 1) Record concomitant medications
- 2) Review any adverse events
- 3) Vital signs including weight.
- 4) Labs: CBC with Diff, Chem 20 and IgG levels, serum pregnancy test for women of childbearing potential. IgA levels will be drawn as screening only.
- 5) Distribute study medication.
- 6) TSQM



- 7) Instructions in subcutaneous injections will be given by either the study coordinator or the designee.

*Screening and Informed Consent (Week [-10]):* Patients identified as a potential candidate will sign informed consent and will undergo a complete blood count (CBC), chemistry profile (Chem 20) and IgG levels, IgA levels, general physical and neurological examination, serum pregnancy test, vital signs including weight, and MGFA. If the inclusion criteria are met, the patient can be entered into the study. Women of child bearing potential will be instructed to take proper precautions to avoid pregnancy for three months after stopping the study medication. When inclusion/exclusion criteria are met, protocol eligibility and admission information consisting of demographic data including age, sex, past medical history, concomitant medications including prednisone dose, and prior AChR-Ab and MuSK Ab result on each patient will be documented. This visit can occur within 4 weeks of the subject's first IVIg stabilization.

*Screening Phase: IVIg Infusion Stabilization Weeks [-9, -5 and -1])*

Subjects will be asked to refrain from taking pyridostigmine for at least 12 hours prior to testing. Once testing is completed pyridostigmine may be restarted. Pre-medications may be administered if the patient has had adverse reaction prior to study entry while on IVIg or if they developed such events during study drug administration. These will be captured and followed in the concomitant medication log. All study visit procedures must be performed prior to infusion. These procedures include for all three visits QMG (including FVC), and MG-ADL, adverse events, concomitant medications, vital signs including weight, safety labs and a general physical exam. Additionally, MG composite score (including MMT), and MG-QOL-15 will be done at the Week -9 visit.

*Experimental Treatment Phase:*

*Baseline Visit (within 1 week of the last screening phase IVIg infusion) (Week 0):*

Within 1 week of the last infusion of the Screening Phase, patients will be instructed at baseline not to take pyridostigmine for at least 12 hours prior to all visits. Pyridostigmine may be restarted after testing is completed. All study visit procedures will be performed prior to infusion. These procedures include QMG (including FVC), MG-ADL, MG composite score (including MMT), and MG-QOL-15, adverse events and concomitant medications, vital signs including weight, safety labs, general physical examination, neurological examination, and the TSQM.

Treatment Satisfaction Questionnaire for Medication (TSQM) is a generic measure of treatment satisfaction for medication. It has undergone rigorous development with sound psychometric properties and is available in multiple linguistically validated languages. The domains tested include effectiveness, side effects, convenience and global satisfaction.<sup>57-58</sup> We will be using the TSQM version II for this study.

Instruction on subcutaneous injection will be given by the study coordinator or designee at the baseline visit. The subjects must return for baseline day 2 (Week 0.1) the day immediately following baseline day 1 (Week 0, first SCIg infusion). At this visit the subject will be evaluated on their ability to self-administer the subcutaneous injections. If the subject is still not comfortable, or the site personnel determine the subject needs additional training the subject may return for additional visits Week 0.2, and 0.3 if necessary.

*Week 1:*

Subjects will return the first week to assess how effective they are in performing their own subcutaneous infusion. Additionally, a general physical exam, vital signs including weight, safety labs, and a review of the subject's concomitant medications and adverse events will be done at this visit.

*Week 2 and 3:*

The study coordinator will contact the subject to evaluate if they are having trouble performing their subcutaneous infusions. The subjects may return for more education if needed.

*Follow-up Visits (Weeks 4, 8 and 12)*

Patients will be instructed not to take pyridostigmine for at least 12 hours prior to each evaluation. Patient visits will be carried out at each institution's General Clinical Research Center (GCRC) or other facilities suitable for clinical research.

Every four weeks, the CE will perform the following tests:

- 1) Quantitative MG score (including FVC).
- 2) MG ADL (Activities of Daily Living) score.
- 3) MG Composite score (including MMT).
- 4) MG QOL-15.

Every four weeks the study investigator will perform the following:

- 1) History and physical exam.
- 2) Neurological examination (Week 12)
- 3) MGFA MG grade (Week 12 only).

The study coordinator will perform the following every month:

- 1) Review any adverse events
- 2) Review concomitant medications
- 3) Vital signs, including weight.
- 4) CBC and Chem 20, IgG levels
- 5) Serum pregnancy test for women of childbearing potential.
- 6) Collect unused medication, reconcile drug usage
- 7) Distribute study medication at month 3 only
- 8) TSQM at Week 12 only

*Week 6:*

This is an added safety visit. Subjects will return to have infusion sites inspected prior to dose escalation per site above 40 cc per site. If there is no residual reaction at sites other than mild erythema or induration, the volume per site would be advanced, as tolerated. If this escalation occurs at another time interval, an unscheduled visit will be performed.

*Week 13:*

This is a completion visit that will be conducted in-person one week after SCIg treatment is completed. Adverse events will be reviewed and closed if resolved. Safety labs will be draw only if results were clinically significant at Week 12, vital signs including weight and a general physical exam will be done.

*Unscheduled Visits:*

Unscheduled visits may be done for subject difficulty with subcutaneous drug administration, intolerable adverse events or for suspected worsening.

If the subject appears to have trouble with administering the subcutaneous medication, you may bring the subject in for as many visits as necessary.

If the subject appears to have an intolerable adverse event, you may bring the subject in for as many visits as necessary if these cannot be addressed by a phone call.

If the subject reports suspected worsening in between visits, you may bring the subject in. Testing at unscheduled visits is done only to assess for clinical worsening via QMG and MG-ADL. If no worsening is found, patients will continue to be a part of the study. If a patient experiences a worsening event that does not qualify as clinical deterioration (per pg. 22) and the investigator determines it is safe for that patient to continue, the patient will remain in the study. On the other hand, if a patient experiences a worsening event that qualifies as clinical deterioration the patient will be withdrawn from the study.

*End of Study Visit Follow Up Calls (Week 14, 16):* The study coordinator will call each subject bi-monthly for one month to close out all study drug related adverse events still open. Ongoing active AEs will be considered permanent after the one month follow up.

*Concomitant Medication:* Every effort should be made to keep subjects on a stable treatment regimen through Week 16. The study coordinator will obtain at each visit, the current list of concomitant medication. See *Subject deterioration and rescue medication* section below for guidance.

*Medication Reconciliation:* Records of all SCIg study drug dispensed and returned dosages administered, and intervals between visits will be kept during the study. Subjects will be asked to return all unused medication at each visit and at the end of the study.

*Adverse Events:* Adverse events (AE) will be reported using FDA guidance *Safety Reporting Requirements for INDs and BA/BE Studies*. AEs will be grouped into the following categories:

A. Adverse Event (21 CFR 312.32(a))

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related

B. Suspected Adverse Reaction (21 CFR 312.32(a))

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### C. Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

#### *Severity of Adverse Events*

The severity of each AE is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Severity Intensity Scale for Adverse Event Terminology.

Common Terminology Criteria for Adverse Events v4.0 (CTCAE) coding dictionary will be used for data entry in the CRIS/VELOS electronic database system for adverse event classification using the above CDISC criteria.

#### *Causality of Adverse Events*

The causal relationship of an AE to IgPro20 should always be assessed by the investigator. Even if the investigator considers that there is no causal relationship to IgPro20, the AE must still be reported.

One of the following categories will be used for assessing the causal relationship of each AE, including a laboratory test abnormality, to IgPro20:

- *Not Related*
  - Event or laboratory test abnormality with a time to IgPro20 intake that makes a relationship impossible.
  - Is most likely explained by concurrent disease or other drugs or chemicals (either pathophysiologically or clinically).
  - Has occurred prior to administration of IgPro20 in comparable severity and/or frequency.
- *Related*
  - Event or laboratory test abnormality with plausible time relationship to IgPro20 intake.
  - Cannot be explained by disease or other drugs.
  - Response to withdrawal plausible (pharmacologically, pathologically).
  - Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon).
  - Rechallenge satisfactory, if necessary.

The degree of certainty with which an AE is attributed to IgPro20 or an alternative cause (e.g., natural history of the underlying disease, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of:

- Known pharmacology of IgPro20.
- Clinically and/or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related e.g., headache, facial flushing, and pallor.
- Plausibility supported by the temporal relationship e.g., the event being related by time to administration or termination of treatment with IgPro20, drug withdrawal, or reproduced on rechallenge.

#### D. Unexpected (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### E. Serious (21 CFR 312.32(a))

A serious adverse event is defined as:

1. Death;
2. Life-threatening (report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death);
3. Hospitalization for any reason;
4. Disability (report if the adverse event resulted in a significant; persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life;
5. Congenital anomaly (report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child);
6. Requires intervention to prevent permanent impairment or damage (report if you suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient).

The PI or Co-I will monitor AEs monthly, grade them, and indicate if the AE is related to the study medication (definite, probable, possible, unlikely, not related). For each AE, the PI will determine if the study medication should be continued. Patients will be instructed to call the PI's office (or on-call resident if at night or on the weekend) to report events that occur between study visits. All SAEs will be reported to the medical monitor, HSC, Clinical Research Center (if applicable), and FDA per guidelines, as soon as possible, but no later than five working days.

#### *Hemolysis Risk:*

Cases of hemolysis can occur in treatment with IgPro20. If a subject experiences a confirmed hemolysis requiring transfusion or medical intervention (e.g. steroids), experiences

catastrophic consequences of hemolysis (e.g. renal failure, hypotension, bronchospasm, emergency splenectomy), or death during the study, the subject should be withdrawn. Hemolysis of this nature will be considered an expected serious adverse event.

### *Thrombosis Risk:*

#### **Clinical Findings**

- ☐ Paralysis, paresis or recent orthopedic casting of lower extremity (1 point)
- ☐ Recently bedridden (more than 3 days) or major surgery within past 4 weeks (1 point)
- ☐ Localized tenderness in deep vein system (1 point)
- ☐ Swelling of entire leg (1 point)
- ☐ Calf swelling 3 cm greater than other leg (measured 10 cm below the tibial tuberosity) (1 point)
- ☐ Pitting edema greater in the symptomatic leg (1 point)
- ☐ Collateral non- varicose superficial veins (1 point)
- ☐ Active cancer or cancer treated within 6 months (1 point)
- ☐ Alternative diagnosis more likely than DVT (Baker's cyst, cellulitis, muscle damage, superficial venous thrombosis, post phlebitic syndrome, inguinal lymphadenopathy, external venous compression) (-2 points)

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity). Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits, and chest pain and should be advised to contact their physician immediately upon onset of symptoms. Patients should be sufficiently hydrated before use of immunoglobulins.

If patient is suspected to have deep vein thrombosis, such as new calf swelling or calf pain, we will apply Wells' pretest probability scoring as outlined below and the Wells' pretest probability scoring form (see appendix 2) should be completed as source documentation.<sup>59</sup> Subjects will be examined for possible thromboembolic events at each visit. In any subject in whom the history or routine physical exam suggests the possibility of DVT, a detailed examination will be performed and the Wells score will be calculated according to the online Calculator below.<sup>60</sup>

Calculator: DVT probability: Wells score system

Total

Criteria

Point

Count:

[Reset Form](#)

## DVT Risk Score Interpretation

<b>3-8 Points:</b>	High probability of DVT
<b>1-2 Points:</b>	Moderate probability
<b>-2-0 Points:</b>	Low Probability

In any subject with a Wells' score higher than 2.0, further evaluation will be performed according to the 2012 ACCP Guidelines<sup>61</sup> for "Diagnosis of DVT- Antithrombotic Therapy and Prevention of Thrombosis." For scores of 1.0 to 2.0, we will exert an abundance of caution by obtaining a D-dimer, and if that is normal proceed with close follow up and reevaluation at the next visit. If D-dimer is abnormal (defined as elevated above the upper limit of normal), we will pursue leg sonogram.

### *Renal Failure Risk:*

Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human immune globulin products. We will ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Hizentra and at appropriate intervals thereafter. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure. If renal function deteriorates, we will consider discontinuing Hizentra. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), we plan to administer Hizentra at the minimum rate practicable.

### *Transfusion-Related Acute Lung Injury (TRALI):*

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

We will monitor drug recipients for pulmonary adverse reactions. If TRALI is suspected, We will perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

*Procedures:*

Elective procedures that were pre-planned prior to the time that written informed consent was obtained are not AEs. Any complication or worsening of a preexisting condition leading to the procedure must be considered an AE. In addition, any AE that could occur as an outcome of the planned procedure should be considered as an AE.

Diagnostic and therapeutic procedures (invasive and non-invasive) such as surgery or angiography should not be reported as an AE or SAE. However, the medical condition or the diagnosis that was responsible for the procedure should be recorded. The procedure should be recorded in the narrative as treatment for the AE or SAE (e.g., laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder).

*Laboratory monitoring:*

The frequency of safety laboratory testing is monthly. Besides, complete blood count, IgG levels and complete metabolic panel, we are obtaining direct antiglobulin (Coombs) testing and reticulocyte count. We will therefore screen for hemolysis with CBC, Coombs, unconjugated bilirubin and reticulocytes. If there is unexplained new anemia as evidenced by hemoglobin decrease by  $\geq 2\text{g/dL}$ , or if the history or physical suggest any symptoms of hemolysis such as tachycardia, shortness of breath, dark urine or jaundiced appearance, or positive result of direct antiglobulin test or increased reticulocyte count, hemolysis will be confirmed via low haptoglobin level.

*Treatment Failures*

Treatment failure will be defined as any one or more of the following during the SCIg Treatment Phase:

- 1) Progression of respiratory insufficiency such that the subject requires mechanical ventilation.
- 2) Progression of dysphagia so that the subject has frequent choking and requires mechanical feeding.
- 3) The investigator believes the subject has deteriorated to the point that, despite an up titration of SCIg to 1.37 fold the original IVIg dose, a new immunotherapy is needed (except for prednisone). The time to initiation or increase of the new immunotherapy will be documented.
- 4) The patient is unwilling to continue in the study because of progressive or continuing disability.
- 5) The patient's study physician feels that it would not be in the best interest of the patient to continue in the study due to MG symptoms.

*Subject Withdrawal:*

Patients will withdraw from the study during the IV or SC phase if they meet any of the above treatment failure criteria. We will monitor renal function monthly and if there is an elevation in creatinine  $> 1.7\text{ mg/dL}$ , the patient will be withdrawn.

In addition, subjects will be withdrawn from the study if there is a change in IVIg dose during the ISP (IVIg Stabilization Phase) as compared to the entry (Week -9) dose.



*Subject deterioration, worsening, rescue medication and improvement:*

Subjects may experience clinical deterioration, clinical worsening (that does not qualify as deterioration), and clinical improvement or disease stability.

Subjects may withdraw at any point during the course of the study. For this protocol, clinical deterioration is defined as one the following:

- 1) Subjects who experience an MG crisis, which is defined as weakness from MG that is severe enough to necessitate intubation or to delay extubation following surgery. The respiratory failure is due to weakness of respiratory muscles, severe bulbar (oropharyngeal) muscle weakness, or may be the predominant feature in some subjects. Or
- 2) Significant symptomatic worsening to a score of 3 or a 2-point worsening on any one of the individual MG-ADL items other than double vision or eyelid droop in comparison to Week -9 in the IVIg screening phase and in comparison to Week 0 in the experimental treatment phase. Or
- 3) Subjects for whom the treating physician believes that the subject's health is in jeopardy if rescue therapy is not given (for example emergency situations).

Patients experiencing a clinical deterioration are also considered treatment failures and are withdrawn from the screening phase or experimental treatment phase as applicable. Treatment of clinical deterioration is per standard of care with plasmapheresis or IVIg. These patients will be withdrawn from the study and are treatment failures.

For this protocol, clinical worsening is defined as one the following:

- 1) Patient worsening that does not qualify as a clinical deterioration. Or
- 2) Significant symptomatic worsening to a score of 3 or a 2-point worsening on the double vision or eyelid droop items of MG-ADL in comparison to Week -9 in the IVIg screening phase and in comparison to Week 0 in the experimental treatment phase. Or
- 3) Increase in total QMG score by more than 3 points in comparison to Week -9 in the IVIg screening phase and in comparison, to Week 0 in the experimental treatment phase

For patients that are withdrawn by the investigator due worsening that does not qualify as deterioration or for personal reasons (travel or family situation), rescue medication includes increasing or instituting prednisone or adjuvant immunosuppressive therapy as well as restarting previously effective IVIg per standard of medical care and based on the treating physician best judgment. If the subject wish to withdraw at their own request due perceived worsening that does not qualify as deterioration, the investigator will offer them a treatment plan that would allow them continued study participation (see below).

For patients who are experiencing a worsening that does not qualify as a clinical deterioration and in whom the investigator assesses it is safe to continue with study participation, acceptable rescue medications include the initiation of prednisone or mestinon or an increase in SCIg, prednisone or mestinon dose. We do not consider subjects with less severe worsening requiring an increase in concomitant medication to be either withdrawals or treatment failures. Since MG is a variable disease from week to week, it would not be unusual in the course of the study that the dose of other medications such as prednisone be changed based on disease status and adverse events. The SCIg dose may be increased by 25% (from 1.20x to 1.37x the IVIg dose at week 4). Patients requiring increase in SCIg dose or other treatments (prednisone or mestinon) will undergo additional assessment at unscheduled visits. Other alternatives are that the prednisone dose may be increased, or if

the investigator determines it is appropriate (for example worsening ptosis) that the patient be closely followed up until clinical condition reassessment at the next visit. The exact prednisone increase schedule is left up to the local site investigator judgment. As an example, for patients on  $\geq 15$  mg daily or the equivalent for every other day dosing, it is suggested that the prednisone daily dose be increased by 20 mg. For patients on  $< 15$  mg daily or the equivalent for every other day dosing, it is suggested that prednisone be increased by 10 or 20 mg, at the physician's discretion. Further increments in dose are at the physician's discretion. However, the exact prednisone increase schedule is left up to the local site investigator judgment.

The exact prednisone tapering schedule is left up to the local site investigator judgment. For subjects taking prednisone every other day, below is **an example** of a monthly tapering schedule:

Every other day dose (mg)	Taper to
120	100
100	80
80	60
60	40
40	30
30	20
20	15
15	10
10	7.5
7.5	5.0
5.0	2.5
2.5	0

The exact prednisone tapering schedule is left up to the local site investigator judgment. For subjects taking prednisone daily, below is an **example** of a monthly tapering schedule:

Daily dose (mg)	Taper to
60	50
50	40
40	30
30	20
20	15
15	10
10	7.5
7.5	5
5	3
3	2
2	1
1	0

In subjects that do not fulfill criteria for worsening or deterioration, clinical improvement in the experimental treatment phase is defined as one the following at Week 12 compared to Week 0:1) Improvement (decrease) in the MG-ADL by 2 or more points Or

2) Improvement (decrease) in total QMG score by 3 or more points

Finally, subjects that do not fulfill criteria for worsening, deterioration or clinical improvement at Week 12 compared to Week 0 are considered to have stable MG disease.

*Study timeline:*

*Year 1: Write manual of operations and study forms, develop computerized CRIS Database and install at all sites, including training, complete IRB approval for all center, hold a start of study meeting, do training and reliability testing for investigators, evaluators, and coordinators, send out supplies.*

*Year 2: Begin recruiting subjects.*

*Year 3: Complete the subjects enrolled continue the yearly site audits, cleaning up the data, data analysis. Meeting presentation and drafting manuscript.*

*Data Analysis Plan and Statistical Considerations:*

*1. Analysis of Primary Outcome:*

At the end of the 9-week IVIg screening phase, baseline QMG scores of all the patients will be recorded. At the end of SCIg experimental treatment phase (Week 12), the QMG score will be captured and compared to Week 0. If the increase in QMG scores from Week 0 to Week 12 in the experimental treatment phase is found to be no more than 3 points, then they will be considered to be a 'success' in terms of their response. We hypothesize that the positive response rate of these patients is at least 70%. Allowing a margin of 5%, our hypotheses are formally stated below:

Null hypothesis  $H_0$ : Proportion of patients whose QMG scores are increased by more than 3 points at the end of the SCIg treatment phase  $\leq 0.65$

Alternate hypothesis  $H_A$ : Proportion of patients whose QMG scores are increased by no more than 3 points at the end of the SCIg treatment phase  $> 0.65$

This hypothesis will be tested using a one sided one sample test of proportions with the normal approximation, at the 5% significance level. We will also report a 95% confidence interval for the true proportion of subjects who experience a 'success' as with a sample size of 25 patients, we will have a margin of error of 0.19. In the experimental treatment phase, patients who either experience treatment failure (as previously defined on pg. 22) or clinical deterioration (as defined above on pg. 22) will be withdrawn before Week 12 and we will therefore impute for both non-positive responses at Week 12, a discrete QMG score increase of more than 3 points. For example, if the largest deterioration score observed is 8, then a QMG score ranging between 4 and 8 will be imputed at Week 12. Although we do not expect many missing observations at Week 12 of the SCIg phase, the outcomes recorded at these intermediate time points will allow us the ability to impute data at this endpoint. Specifically, in the case where no outcome is available for a subject at Week 12 due to the subject's perception of a worsened condition, we will impute for this subject a QMG score increase at Week 12 of more than 3 points. In cases where subjects refuse to proceed to Week 12 or are lost to follow-up even though they were responding well on the treatment (as evidenced by the intermediate measurements), we will impute their Week 12 observation using the last observation carried forward (LOCF) approach. We will complement our LOCF approach with sensitivity analyses covering the following alternate approaches: (1) Multiple imputation with

5 replicates per imputation to account for the uncertainty inherent to the imputation (2) Mixed model calculations accounting for the trend in QMG values over time (3) Best case and worst case scenarios.

## *2. Additional Exploratory Analysis of Primary Outcomes:*

Additional exploratory analysis will be carried out treating QMG scores at baseline, Week 4, Week 8 and Week 12, as a continuous response variable. Descriptive statistics will be reported using means and standard deviations if the distribution of QMG scores is found to be normal and using medians and interquartile range if they are found to be non-normal. One advantage of reporting scores at the intermediate weeks is that it will allow us to assess whether or not some patients on SCIg stabilize early in terms of the QMG scores. It will also allow us to study the trend over time in an exploratory manner. We will further complement our exploratory analysis by conducting a two-sided non-parametric signed rank test in order to assess whether the QMG scores changed significantly after switching from IVIg to SCIg. Also, we will dichotomize the QMG into two groups (high and low) based on clinically relevant thresholds and compare the differences in proportions at end of study and baseline.

## *3. Analysis of Secondary Outcomes:*

Analysis of secondary outcome measures as listed in the Aims section such as MG-ADL, MG QOL-15, the MG composite score and TSQM will primarily be conducted only for those who complete the study. We will conduct a two-sided signed-rank test to assess whether these scores changed significantly from baseline (Week 0) to Week 12. In case of missing values for the MG-ADL, MG QOL-15, and the MG composite score in cases where subjects refuse to proceed to Week 12 even though they were responding well on the treatment (as evidenced by the intermediate measurements) or are lost to follow-up, we will impute their Week 12 observation using the last observation carried forward (LOCF) approach. We will also report the proportion of subjects enrolled in the subcutaneous experimental treatment study phase (Week 0 to Week 12) fulfilling our definition of improvement (as mentioned on pg. 24) along with a 95% confidence interval. We will compare between the two phases the percent of subjects meeting the definition of deterioration, worsening, stability and improvement. We will analyze the effect of prednisone dosage (Increase vs Not Increased) on clinical improvement (Yes vs No) using a 2x2 Fisher's exact test in the SCIg phase of the study by comparing dose levels at Week 12 to Week 0 for those patients who complete Week 12 of the study. To do this, we will ask the patients at Week 0, Week 4, Week 8 and Week 12 about their prednisone dosage levels. Those patients who exit the study prematurely due to deterioration before Week 12 will be excluded from this Fisher's test calculations. In the event that the Week 12 prednisone dose observation is missing even when patients have completed Week 12 (QMG or MGADL done), we will use the LOCF approach to impute this missing value as long as at the last available assessment, the patient was deemed to be improving (in terms of QMG or MGADL scores as defined under "Subject deterioration, worsening, rescue medication and improvement"). A two-sided signed-rank test will be also conducted to assess whether IgG levels changed significantly between the intravenous screening phase (Week -10 to Week 0) to the subcutaneous experimental treatment study phase (Week 1 to Week 12). All tests will be conducted at the 5% level of significance. For the secondary outcome measures related to monitoring the safety profile of patients between the two study phases, a similar test will be conducted when the safety parameters measured are continuous variables and a one sample test for the difference in proportions will be conducted when they are measured as treatment-related

severity rates. The comparison epochs for safety are also between the intravenous screening phase (Week -10 to Week 0) and the subcutaneous experimental treatment study phase (Week 0 [after first SCIg dose] to Week 12). Adverse events occurring in the two phases (mild, moderate/severe) will be summarized using a McNemar's test.

#### *4. Sample Size Considerations:*

With a sample size of 25 patients, we have at least 70% power to detect a success rate of 85% or higher using the chi-square test compared to an expected success rate of 65% or lower. We anticipate we will be able to assess efficacy, safety and tolerability of SCIg with the current sample size over 12 weeks and compare that these parameters to the 12 week IVIg phase. The selected sample size will enable us to complete study enrollment with the current number of sites.

MG is a rare disease and MG studies have consistently experienced difficulty enrolling subjects due to a multiplicity of poorly understood reasons.<sup>34</sup> In the Methotrexate study of MG and similar to other previous MG studies, enrollment has been a challenge. However, we managed to complete enrollment of 50 subjects by adding sites. In the current SCIg study protocol, the eligible study population is narrowed due to the inclusion criterion requiring MG cases to be on stable IVIg doses. While 85 to 90% of MG patients are seropositive for either the AchR or MuSK autoantibodies, some of these cases are treated in clinical practice with IVIg maintenance. Based on the pre-site selection feasibility survey, 25 subjects is a reasonable and achievable goal with the selected five sites. If enrollment is found to be slower than predicted, we are ready to add more sites to complete this study.

#### *5. Study Populations:*

**Safety population:** All patients enrolled at baseline constitute the safety population. The subjects in this population will included in the analysis of adverse events, vital signs, clinical laboratory findings, and other safety data. But for the purpose of statistical analyses, the rates of adverse events experienced by these subjects in the SCIg phase will be compared to the rates experienced during the IVIg phase of the study. Adverse events will be tabulated by treatment group, severity, and perceived relationship to study drug. For each adverse event, the treatment groups will be compared regarding the occurrence of at least one event using the Fisher's exact test. The comparisons will be repeated excluding all mild symptoms. Continuous measures such as vital signs and laboratory test results will be analyzed in a manner similar to that for the primary outcome variable.

**Intent to treat population (ITT):** Only those patients who receive at least one dose of SCIg are considered to be the primary population which is the same as ITT population. The ITT will be included in the analysis of baseline findings and efficacy results. Only those patients who receive at least one dose of SCIg are considered to be the primary population and the intent-to-treat population.

**Unscheduled visits:** In the event that there are unscheduled patient visits, we will report the frequency of such visits for the two phases of the study. We will also document the date and reason for such visits and assess if these visits are systematic or random. If occurrence of

such visits is due to side effects we will compare the rates of such events across the two phases of the study. Testing at unscheduled visits is done only to check and assess clinical worsening. If no worsening is found, patients will continue to be a part of the study. If a patient experiences a worsening event that does not qualify as clinical deterioration (per pg. 22) and the investigator determines it is safe for that patient to continue, the patient will remain in the study. On the other hand, if a patient experiences a worsening event that qualifies as clinical deterioration the patient will be withdrawn from the study. We will compare the within-person variation to the cross-person variation for the overall data. If the within-person variation is found to be less than the cross-person variation, we will use a LOCF approach to impute the patient's QMG score at the next time point and do a sign rank test on that time point and baseline. On the other hand, if the within-person variation is found to be greater than the cross-person variation, we will impute the observation at the next time point followed by a sign rank test.

SAS 9.4 will be used for all analyses. All data management and statistical analysis will be performed in the Department of Biostatistics at the University of Kansas Medical Center. The Velos Clinical Research Information System (CRIS) will be used at all sites to enter and view data. This will be available to the safety monitors (see below).

#### *Safety Monitoring*

Subjects will be interviewed at each visit about possible side effects of medications and MG-related symptoms. Complete blood count (CBC) with differential, chemistry profile (Chem 20) including liver and renal function, direct antiglobulin (Coombs) testing and reticulocyte count will be performed at each visit. We will therefore screen for hemolysis with CBC, Coombs, unconjugated bilirubin and reticulocytes. If there is unexplained new anemia or positive result of direct antiglobulin test or increased reticulocyte count, hemolysis will be confirmed via low haptoglobin level. Safety will also be assessed by physical examinations and evaluations of vital signs at clinic visits. The site investigator will then evaluate any changes and determine the need for any intervention.

#### *Data Safety Monitoring Committee*

A data safety monitoring committee will be established through the University of Kansas Medical Center Office of Compliance. The DSMB will meet every 4 months by phone to review recruitment, adverse events, and serious adverse events. They will meet with the study statistician and medical monitor prior to the meeting to review the event reports and identify any issues that need to be addressed.

#### *Annual Site Monitoring*

Patient safety will be a top priority and adverse events will be closely monitored. Patients will be provided phone numbers on the consent forms so they can reach investigators at any time should problems arise. Study forms have been designed to record adverse events and document actions taken when they occur. Criteria have been established for treatment failures, and patients will be treated appropriately should their disease progress during the course of the study.

#### *Stopping Rule*

Taking into account patient safety considerations, following stopping rules will be incorporated based on a binomial calculator assuming >65% treatment success rate.

- (1) Treatment failures in  $\geq 5$  subjects in the first 10 subjects
- (2) Treatment failures in  $> 7$  subjects in the first 14 subjects
- (3) Treatment failures in  $> 8$  subjects in the first 17 subjects
- (4) Treatment failures in  $> 9$  subjects in the first 20 subjects if additional patients (more than 20) are recruited in the study

The number of these events will be tracked by the Department of Biostatistics at the University of Kansas Medical Center.

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**Table 1: Study Visits**

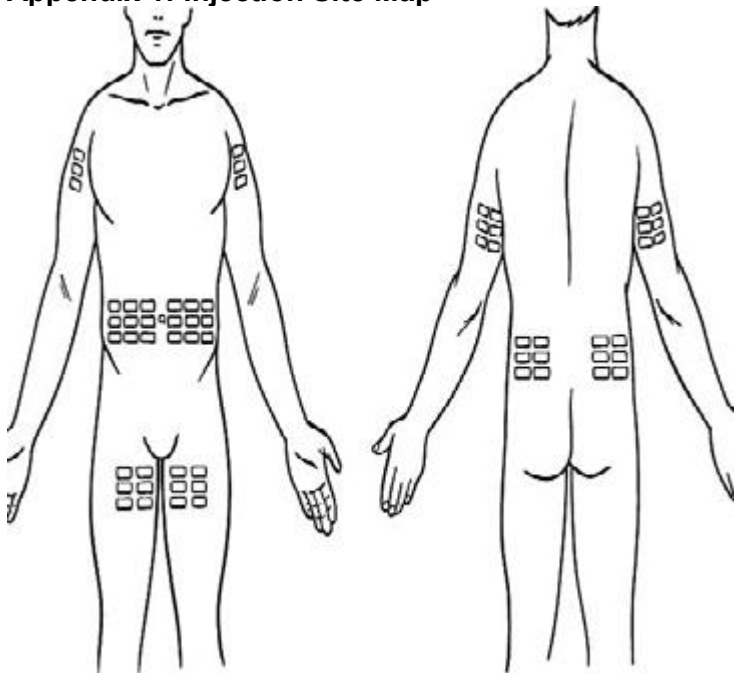
	Screening Phase					Experimental Treatment Phase													
Week	-10 (Screen)	-9 1 <sup>st</sup> IVIg stabilization	-5 2nd IVIg stabilization	-1 3 <sup>rd</sup> IVIg stabilization	0 Baseline	0.1	0.2	0.3	1	2 ****	3 ****	4	6	8	12	13	14 ****	16 ****	
Consent form	X																		
Medical History	X																		
Vital Signs (including weight)	X	X	X	X	X	X			X			X		X	X	X			
General Physical Examination	X	X	X	X	X				X			X		X	X	X			
Neurological Examination	X				X										X				
Infusion at research facility		X	X	X															
Subcu instruction/infusion at research facility					X	X	X	X	X	X	X								
Safety labs*	X		X	X	X				X			X		X	X	X*			
IgA level evaluation	X																		
Serum Pregnancy Test**	X				X							X		X	X				
Concomitant Medication	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	
Dispensing of Medication									X			X		X					
Medication collection and reconciliation												X		X	X	X			
MGFA	X				X										X				
QMG (including FVC)		X	X	X	X							X		X	X				
MG-ADL		X	X	X	X							X		X	X				
MG Composite Score (including MMT)		X			X							X		X	X				
MG-QOL-15		X			X							X		X	X				
TSQM					X										X				
Adverse Events		X	X	X	X				X	X	X	X	X	X	X	X	X	X	
Phone Call/Email ****										X	X						X	X	

\* = Full Safety Labs: Complete blood count (CBC) with differential, complete metabolic panel, serum IgG level, direct antiglobulin test and reticulocyte count. Safety labs will only be drawn at Week 13 if clinically significant at Week 12.

\*\* = Serum pregnancy test for women of child-bearing potential.

\*\*\*\* = Phone Call/Email to assess how subject is doing administering medication/Optional in person visit

## Appendix 1: Injection Site Map



**Appendix 2: Probability Scoring for DVT****Wells' Pretest Probability Scoring Form**

Site:	Subject ID:	Date:	Visit Week:
-------	-------------	-------	-------------

Clinical feature	Points	Patient score
Active cancer (treatment ongoing, within 6 months, or palliative)	1	
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1	
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1	
Localised tenderness along the distribution of the deep venous system	1	
Entire leg swollen	1	
Calf swelling at least 3 cm larger than asymptomatic side	1	
Pitting oedema confined to the symptomatic leg	1	
Collateral superficial veins (non-varicose)	1	
Previously documented DVT	1	
An alternative diagnosis is at least as likely as DVT	-2	
Total Score		
<b>Clinical probability simplified score</b>		
High Probability of DVT	3-8 points	
Moderate Probability	1-2 points	
Low Probability	-2-0 point	

\_\_\_\_\_  
*PI signature*

Date: \_\_\_\_\_

## Appendix 3: Pocket Reference Risk Card

MG-SCIg	
Rare Serious Risks	Signs & Symptoms
Renal Dysfunction or Failure	Changes in urination. Specifically urinating less and have dark colored urine.
Hemolysis	Fatigued or tired feeling, dizziness, shortness of breath, or rapid heart rate
Thrombosis	New calf swelling, pain or tenderness in the calf
Acute Meningitis	Sudden high fever, severe headache, nausea or vomiting, sensitivity to light, skin rash, stiff neck
Allergic Reaction	Swelling of the face, mouth, lips, gums, tongue, or neck Trouble breathing, cough Rash, or hives Chest tightness Dizziness fainting, fast or weak heartbeat Trouble swallowing, throat tightness, hoarse voice

(Front)

MG-SCIg	
Common effects of Hizentra (SCIg)	Common effects of Privigen (IVIg)
<ul style="list-style-type: none"> <li>• Cough</li> <li>• Rash</li> <li>• Headache</li> <li>• Vomiting</li> <li>• Abdominal pain</li> <li>• Migraine</li> <li>• Itching</li> <li>• Diarrhea</li> <li>• Fatigue</li> <li>• Back pain</li> <li>• Nausea</li> <li>• Pain in extremities</li> <li>• Local reactions (swelling, redness, heat, pain, and itching at injection site)</li> </ul>	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Fatigue</li> <li>• Chills</li> <li>• Vomiting</li> <li>• Back pain</li> <li>• Pain</li> <li>• Elevated body temperature</li> <li>• Abdominal pain</li> <li>• Diarrhea</li> <li>• Cough</li> <li>• Stomach discomfort</li> <li>• Chest pain</li> <li>• Joint swelling</li> <li>• Flu-like illness</li> </ul>

(Back)